REMARKS

The specification has been amended to insert a heading as requested by the Examiner.

Claim 1 has been amended to delete the "preventing or" language.

Claim 3 has been amended to clarify the language of the claim.

Claim 5 has been amended to clarify the language of the claim.

Claims 6 and 8 have been amended to delete language concerning general classes of proteosome inhibitors and to set forth proper Markush language.

Claims 7 and 9 have been amended to set forth proper Markush language and to clarify the language of the claims.

Claims 10-12 have been canceled as being directed to non-elected invention without prejudice to filing a divisional application.

New claim 30 has been added to claim the preferred proteosome inhibitor MG132. Support for this amendment can be found at page 7 of the specification.

It is submitted that these amendments do not constitute new matter, and their entry is requested.

Objection to the Specification

The specification has been amended to insert the heading requested by the Examiner. This amendment obviates this objection, and its withdrawal is requested.

Rejection Under 35 USC § 112, first paragraph

Claims 1-9 and 27-29 were rejected under 35 USC § 112, first paragraph for lack of enablement of the complete scope of the claims, specifically for the lack of enablement for "preventing" diseases associated with endothelial dysfunction. This language has been deleted from the claims.

In view of the above amendment and remarks, it is submitted that the present claimed subject matter is fully enabled by the specification. Withdrawal of this rejection is requested.

Rejection Under 35 USC § 112, first paragraph

Claims 1-9 and 27-29 were rejected under 35 USC § 112, first paragraph for lack of written description. The Examiner contends that the specification does not provide written description for proteosome inhibitors that are expressed in general terms. Applicants do not agree with the Examiner's contention because the terms used in the claims have been associated with proteosome inhibitors in the art. Thus, a skilled artisan readily understands the scope of the claims and recognizes that the inventors had possession of the invention at the time the application was filed. Nevertheless, Applicants have amended the claims so that they refer to proteosome inhibitors generically (claims 1-5 and 27-29) or to specific proteosome inhibitors (claims 6-9 and 30).

Since claims 6-9 and 30 recited specific compounds and specific structures, the specification provides a complete written description of these proteosome inhibitors. In addition, the specification sets forth numerous examples of proteosome inhibitors for use in the claimed method as demonstrated by the amended claims. These numerous proteosome inhibitors clearly convey to the skilled artisan that Applicants were in possession of the genus of proteosome inhibitors for treating diseases associated with endothelial dysfunction at the filing date of the application. Thus, the specification provides a complete written description of the use of proteosome inhibitors for the subject matter of the claimed method.

In view of the above amendments and remarks, it is submitted that the present claimed subject matter is fully described by the specification. Withdrawal of this rejection is requested.

Rejection Under 35 USC § 112, second paragraph

Claims 5 and 6 were rejected under 35 USC § 112, second paragraph for being indefinite. Applicants submit that the amendment of these claims obviates this rejection, and its withdrawal is requested.

Rejection Under 35 USC § 103(a)

Claims 1-6, 8, 9 and 27-29 were rejected under 35 USC § 103(a) as being obvious over Sherman et al. (US 6,096,711). The Examiner contends that Sherman et al. discloses the use of

proteosome inhibitors, such as MG132, in a method of treating pathologies such as ischemic cerebral infarction, ischemic acute renal failure, intestinal ischemia and ischemic heart disease. Although Sherman et al. does not teach nanomolar dosage of the proteosome inhibitor, the Examiner contends that the concentration of a drug is a result-effective variable and thus would have been obvious to optimize the concentration through routine experimentation. The Examiner also contends that since the chemical composition of Sherman et al. is the same as Applicants' composition and thus must have the same properties, at least inherently. Applicants submit that the Examiner is in error in this rejection.

First, Applicants note that Claim 1 has been amended to specify that the administration of the therapeutic effect of at least one proteosome inhibitor is sufficient to produce an enhancement in the expression of eNOS and that this amount is in the nanomolar range. Applicants submit that Sherman et al. does not suggest the claimed method.

Specifically, Sherman et al. teaches that contacting a cell with a proteosome inhibitor, e.g., MG1323, results in an induction of Hsp72 expression in the cell while not committing the cell to apoptotic death. The Hsp72 expression is induced to a level sufficient to suppress stress-activated kinase activity, such as JNK and/or p38 activity. On the basis of this disclosure, Sherman et al. teaches "transiently" administering a proteosome inhibitor to an aged individual for treating pathologies associated with apoptosis and inflammation. The amount of proteosome inhibitor administered is sufficient for inducing Hsp72 production. Sherman et al. discloses using 1.5 mM or 10mM MG132. See, column 12, lines 10-15 and column 11, lines 44-46, respectively. "Transient" exposure is defined at column 4, lines 40-53 as a sufficient concentration for a sufficient length of time to induce Hsp72 production to levels sufficient for suppression of stress-activated kinase activity. Sherman et al. does not disclose the use of a proteosome inhibitor to enhance the expression of eNOS, which enhancement can be long term, i.e., up to ten days, based on a single administered dose that is in the nanomolar range. Thus, Sherman et al. does not disclose or suggest the use of a proteosome inhibitor to enhance the expression of eNOS, which enhancement can be long term, i.e., up to ten days, based on a single administered dose that is in the nanomolar range. In

the absence of any such suggestion in Sherman et al., Applicants submit that Sherman et al. cannot render the presently claimed invention obvious.

Furthermore, Applicants submit that although there may be some desire to optimize the concentration of a given drug as contended by the Examiner, such a desire would relate to the teachings of the prior art, specifically to the method of the prior art in the context of the results obtained by the prior art. As previously discussed, Sherman et al. is directed to contacting a cell with a proteosome inhibitor which results in an induction of Hsp72 expression in the cell to suppress stress-activated kinase activity, such as JNK and/or p38 activity. Thus, any optimization that would be undertaken would be to optimize the dose of the drug to induce the expression of Hsp72 to suppress stress-activated kinase activity and to do so transiently. There is no teaching or suggestion in Sherman that would lead a skilled artisan to optimize a dose of proteosome inhibitor for enhancing the expression of eNOS.

Interestingly, Sherman et al. provides no guidance as to an effective dose range for administering a proteosome inhibitor to induce Hsp72 expression. The only information provided in Sherman et al. is using 1, 1.5 or 2mM MG132 in *in vitro* assays of Hsp72 expression in which the cells are subjected to this concentration for 4.5 or 5 hours. In addition, the cells are pretreated with MG132 to determine the effect on Hsp72 expression. Sherman et al. does not contain any examples that do not perform pretreatment before subjecting to heat shock to test the effect of heat shock on the pretreated cells. There is no showing in Sherman et al. that MG132 is effective in reducing the effects of stress-activated kinase activity subsequent to injury, i.e., using MG132 for treatment. That is, there is no showing that the induction of Hsp72 expression by MG132 could be useful to suppress stress-activated kinase activity by administration after an injury which results in an increase in stress-activated kinase activity. The only optimization that could be suggested by Sherman et al. is an optimization of the amount of MG132 to use for inducing Hsp72 expression.

In addition, there is no teaching or suggestion in Sherman et al. that a proteosome inhibitor can enhance the expression of eNOS. Thus, there is no suggestion that the dose of proteosome inhibitor should be optimized for this effect. This effect, i.e., the enhancement in the expression of eNOS, and the nanomolar dose of proteosome inhibitors are limitations of the claimed subject

matter. Since these limitations are not suggested by Sherman et al., Applicants submit that the claimed subject matter is not rendered obvious by Sherman et al.

Finally, there is nothing in Sherman et al. that would suggest administering the drug for the disclosed purposes in a nanomolar range. In fact, based on the prior art disclosed at page 4 of the present application, Applicants submit that it appears that the prior art would not suggest using a dosage of a proteosome inhibitor at the nanomolar range. There is no suggestion or reasonable prediction in the prior art that a nanomolar dose of at least one proteosome inhibitor would be effective for enhancing the expression of eNOS. There is also no suggestion or reasonable prediction in the prior art that a single administration of such a dose could have a long term enhancement of the expression of eNOS, especially in view of Sherman et al.'s disclosure of a transient effect. Thus, Applicants submit that Sherman et al. does not render the presently claimed invention obvious.

In view of the above amendments and remarks, it is submitted that the present claimed subject matter is not rendered obvious by Sherman et al. Withdrawal of this rejection is requested.

Conclusions

In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,
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